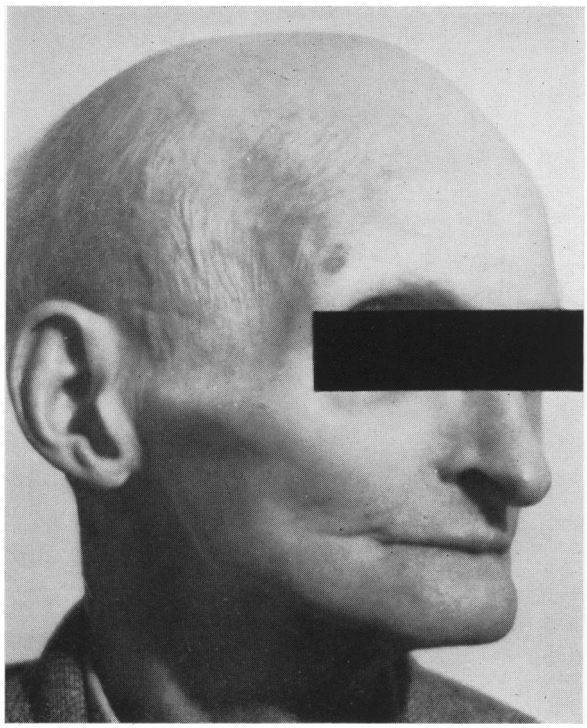

Fig. 1.

Face.—Bird-like appearance, with baldness and premature senility.

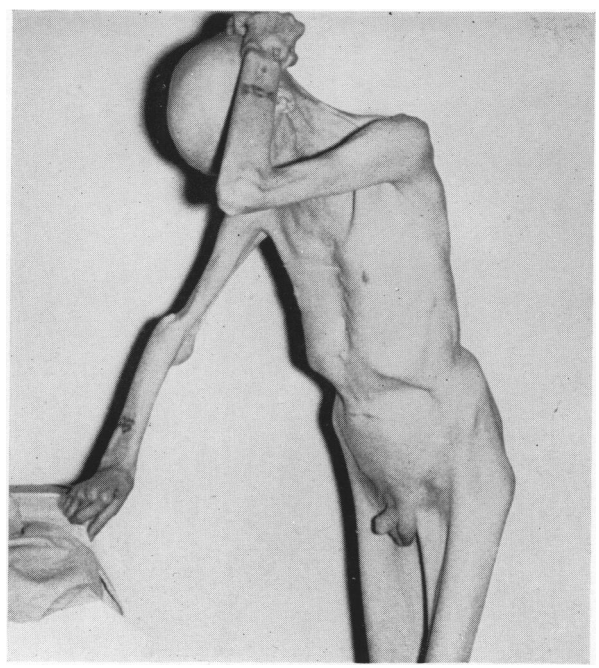

Fig. 2.

Physique.—Body relatively well-nourished compared to marked atrophy of the limbs. Atrophy of the genitals.

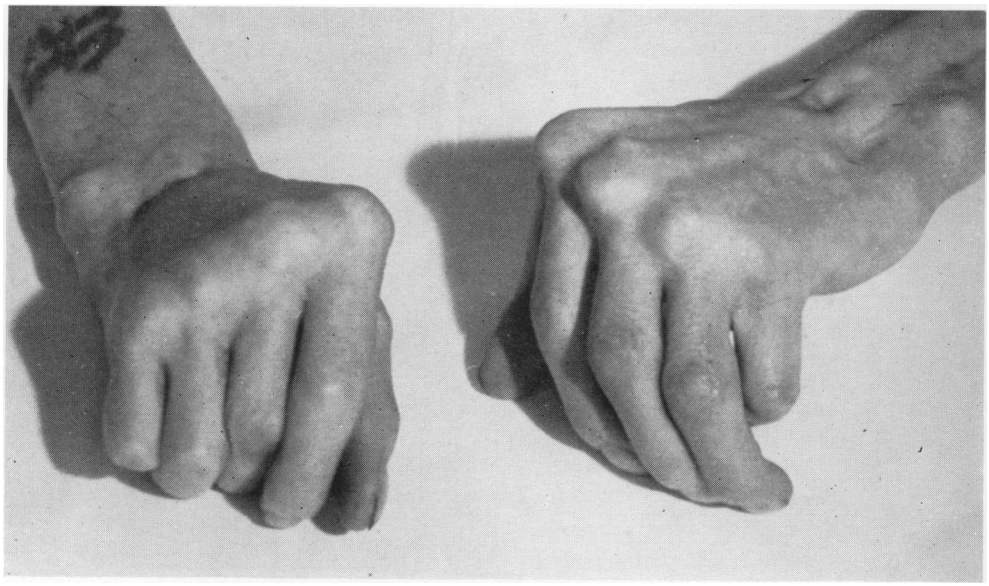

Fig. 3.

Hands.—Marked atrophy of the skin, with ulnar and flexion deformity.

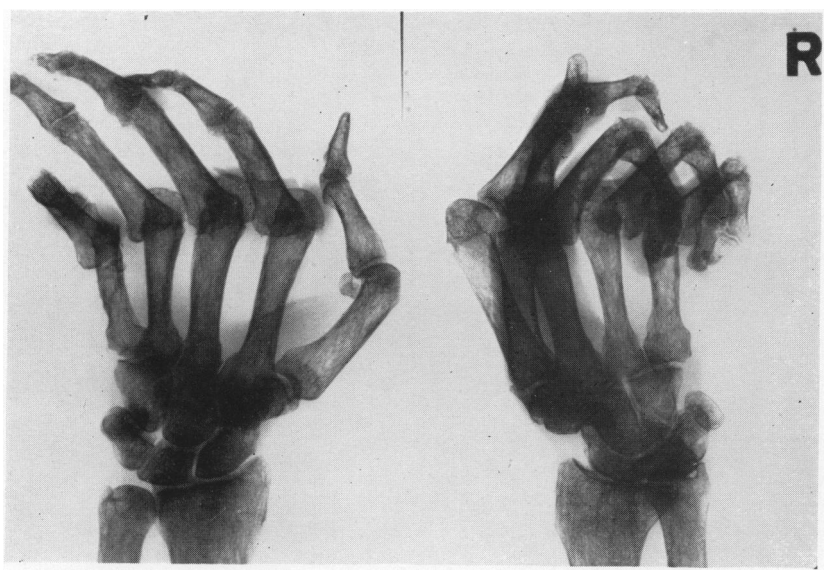

Fig. 4.

X-ray Hands.—Marked osteoporosis, with arthritis and deposits of calcium.

Werner's Syndrome (Progeria in the Adult)

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This syndrome, a generalised abiotrophy involving the whole body, was originally described by Werner in 1904 under the title, "Cataract in Connection with Scleroderma." The condition had occurred in four brothers and sisters. It was associated with presenility, cataracts, atrophic appearance of the skin, and ulceration of the legs which appeared between the second and third decades of life. In a review of the literature up to 1953 Irwin and Ward collected fifty-seven cases, including two of their own. They summarised the characteristics of the syndrome, which are listed below :—

(1) Premature senility.—Premature grey hair (canities), premature baldness, atrophy of the skin, weak high-pitched voice, arteriosclerosis, early cataracts.

(2) Scleroderma-like changes.—Atrophy of the skin and subcutaneous tissues with circumscribed hyperkeratosis. Skin tight over the feet. Ulcers over malleoli, heels, toes, and Achilles tendon.

(3) Characteristic habitus and stature.—Short stature beginning in adolescence, beak-shaped nose, slender extremities.

(4) Other manifestations.—Tendency to diabetes mellitus, hypogonadism, osteoporosis, localised calcification, tendency to occur in siblings.

Illustrative of the foregoing is the case to be reported here. It is a condition which does not appear to be well recognised in these islands, and it is probably commoner than the literature would suggest. Williams, in 1949, reported the only British case recognised as such which we can trace, although this is apparently the second patient from Belfast. The first was discussed by Beath in 1934 under the title, "A Case of Calcinosis Universalis with Premature Senility," and this was probably Werner's syndrome, although the patient lacked cataracts.

Case Record.

A man aged 62 years was admitted in May, 1956, complaining of weakness, coldness, and an inflamed area on the left knee and the left heel.

There was no definite family history suggestive of endocrine disease. His father was killed in 1914 in the Army, his mother died as a young woman, he had two normal sisters and one normal brother.

The symptoms will be reviewed chronologically, although the patient was rather uncertain when his various complaints had actually commenced.

He does not appear to have been backward at school. He then served his time as a moulder, joined the Regular Army and fought in France, where he sustained a shrapnel wound of the right lower thorax, and states that his right eye was

injured and had to be removed in 1919. He married after this, but had no children. He claims that marital relations were satisfactory up to 1949, although this seems doubtful.

About 1930 his voice started to get hoarse in the mornings and gradually became very highly-pitched. He also started to have difficulty in swallowing and maintains that about 1940 his hair became white and then fell out. About this time he noticed lack of strength in his fingers, which became painful at the joints. The arthritis progressed and he developed difficulty in walking. The muscles around the joints became wasted and the hands and feet deformed. Cataract was removed from his remaining eye in 1940.

In 1949 he was admitted to another hospital with a complaint of baldness, arthritis in the arms and legs and a high-pitched voice. He had a right lumbar sympathectomy, and at this time a gangrenous fourth toe on the right side, other toes seem to have been amputated a long time previously.

He was thoroughly investigated with the provisional diagnosis of "hypopituitarism and scleroderma." He was aged then 55 years. He was totally bald, with absent eyebrows and scanty eyelashes. He shaved once weekly. Pubic hair was present in the female distribution, but the axillary hair was scanty. He spoke in a flute-like husky voice. He was very thin around the face, the neck and the limbs, calves being wasted, and there was a small hæmangioma on the outer side of the right eye. Eyeballs were shrunken and the genitalia small in size. The abdomen was protuberant and the body larger in proportion than the limbs. His hands showed deformities at the metacarpal phalangeal and interphalangeal joints with marked ulnar deviation. His elbow joints were even then fixed at 120° of flexion. The ankle joints showed very little mobility and two toes were absent on the right foot and one on the left. His skin was noted to be tightly bound to the subcutaneous tissues over the feet and legs and the elbows. A patch of "scleroderma" was stated to be present over the right elbow and over both feet spreading to the lower $\frac{1}{3}$ of the legs. There was an ulcer over the lateral malleolus which took a considerable time to heal.

He had been in hospitals on several occasions afterwards with similar complaints.

Examination.

There did not appear to have much change from the reports of 1949 onwards. He presented a remarkable appearance (Figs. 1, 2, and 3). He was small in stature with shrunken eyesockets and completely bald, with a beak-like nose. His voice was high-pitched and husky. The elbow joints were fixed, and the hands showed gross ulnar deviation. The feet showed several toes had been removed and movement was very small. Pubic hair was scanty. There was no axillary hair and the testicles and penis were very tiny. The skin was tightly bound down to both the hands and the feet, and owing to his deformities he had not worked since 1944. The subcutaneous tissues were almost absent in the limbs and there were trophic ulcers of the feet, the right shin, and the left knee. The abdomen was protuberant and the skin over the chest more supple than on the limbs. He showed a low blood pressure with a systolic of 100 and a diastolic was not obtained. It

was noted that his pressure in 1949 had been 150/80. In all, he showed signs of marked senility except for the trunk and abdomen, and gave the impression of a plucked bird.

INVESTIGATIONS.

He had been fairly extensively investigated over the years and the results of these are combined for the sake of brevity.

Urinary Gonadotrophins = 4 M.U./24 hours.

Urinary 17-Ketosteroids (24-hour excretion) 2.7 mgs., 5.4 mgs. (and 6.7 mgs. in 1949).

Both these levels are on the low side, particularly the latter, and suggest some pituitary hypofunction.

Insulin sensitivity test showed marked sensitivity with levels of 72, 40, 40, 40, 40, 45, 51, 108, and 105 mgs. per cent.

Glucose tolerance test = Low—normal.

B.M.R. = Plus 4 per cent.

Radioactive Iodine test = Uptake index normal—T = 10.4.

Blood cholesterol = 100 mgs. per cent. (This had been 160 mgs. per cent. in 1949.)

Liver function tests = Serum Proteins—6 gms. per cent.
Albumin 3.6.
Globulin 2.4.

This showed a slight reduction in the albumin which was confirmed on electrophoresis. Previous level in 1949 had been normal.

Thymol Turbidity = 1.

Alkaline Phosphatase = 19.3 K.A. units.

Serum Calcium = 10.1 mgs. per cent. (Same level in 1949.)

Blood urea = 36 mgs. per cent. and 42 mgs. per cent.

Serum Electrolytes showed no abnormality in the sodium, potassium, chlorides or alkali reserve.

E.C.G. = Low voltage. *F.T.M.* = Normal. *Wassermann* = Negative.

B.S.R. = 3 mms. in one hour.

Radiological Examinations.

Skull—Shallow sella turcica.

Both feet—Marked osteoporosis with deformities of the arthritic type and calcinosis circumscripta. Several toes had been amputated.

Pelvis—Some circular areas of rarefaction.

Both hands—Marked osteoporosis and ulnar deformity (Fig. 4).

Barium swallow—There was some degree of pharyngeal dysphagia in that the pharyngeal musculature did not contract and a considerable amount of contrast remained behind trapped in the pyriform fossæ.

Legs—Marked calcification of the right tendon Achilles.

Laryngoscopy—Generalised atrophis changes in the larynx and epiglottis. The cords were pale and did not meet properly owing to lack of tone in the tensors. In places they were injected.

Skin Biopsy (Dr. J. E. Morison)—The skin shows atrophy of the epidermis.

There is some flattening of the papillæ. No skin appendages are present. The distribution of melanin is patchy and the amount varies from area to area. There is no inflammatory infiltrate around blood vessels. The pattern of the elastin in the deeper dermis is preserved, but in the immediately sub-epidermal zone it is atrophic. The appearances are entirely those of gross atrophy and are consistent with progeria and with Werner's syndrome as suggested.

Discussion.

Once the condition is recognised it is probable that many other patients will be studied and reported on, and important clues may be found to the problems of senescence and the waning of intimate cellular metabolism with age. It is for this reason worth considering the syndrome in some detail.

Heredity has been considered to be of great importance, although a familial tendency has not been found in every case (Williams, 1949; Irwin and Ward, 1953; Pomeranz, 1948). Carleton (1943) thought that the condition was heterozygous with a strong suggestion that other genes play a part in determining the expression of the major gene. The relationship to Rothmund's syndrome, a hereditary recessive disorder with cataracts, atrophy of the skin and telangiectasia in early childhood, is certainly close. Tannhauser (1945) has exhaustively gone into this subject. He drew attention to the close relationship with dystrophia myotonica, another familial disorder. Here there is the same age on onset, with cataracts and sexual underdevelopment; but attention is focused on the typical myopathy and the skin changes are not of importance.

The syndrome is, without doubt, distinctive. Although certain variations are found, the senile appearance, the cataracts, the typical habitus and facial appearance with the skin changes are universal. Its basic cause is still uncertain. Oppenheimer and Kugel (1941), who reported the first cases in America, discuss the first autopsy. A primary cancer of the liver was the immediate cause of death, a condition rare enough in itself. The syndrome itself they considered an ectodermal abiotrophy. Atrophy of the testes and prostate, hyperactive thyroid adenomata and parathyroid glands were present with metastatic calcification and osteoporosis, while the pituitary was noted to be normal. Their second case died later from a fibrosarcoma of the radius; another rare tumour. Ectodermal abiotrophy is not enough to explain such a disorder. In hereditary ectodermal dysplasia the condition starts in infancy with atrophy of the skin, baldness, and hyperkeratosis of the palms and soles, but no other disability. Atkins (1954) reports on the post mortem of a case of progeria (Hutchinson-Gilford syndrome). This is another closely related disorder—the child is born normal, there is no obvious hereditary factor, yet within a few years it stops growing and presents an appearance of premature senility. There is a similar facies to Werner's syndrome, loss of hair and fat, arthritic deformities and, in some cases, skin atrophy. Death is usually in adolescence from the results of arteriosclerosis. In the case reported the author could find nothing to support the view that the condition was due to pituitary or pluriglandular deficiency. He found only a slight loss of eosinophils in the pituitary and came to the conclusion there was an enzyme defect in the energy

metabolism cycle producing a mesenchymal dysplasia. It is probable that something similar happens in Werner's syndrome.

Williams (1949) found the 17-ketosteroids normal in his patient, but considered the source to be mainly adrenal, as a high proportion of dehydro-iso-androsterone suggested primary gonadal failure. Gonadal failure is a feature of Werner's syndrome, but its late onset suggests that the primary cause is a multisystem disturbance. Indeed, a woman aged 58 years, who married at 27 and had two children before the menses ceased at 40, is described by Brink and Findlay (1950). She developed grey hair at 18, cataracts at 31, and ulceration of the feet at 43, and although her sons were normal there was consanguinity in her grandparents. She also showed marked phthisis bulbi like the case discussed above, although other cases have been noted to have exophthalmos. Diabetes has been reported in eleven out of fifty-five cases reviewed by Irwin and Ward (1953). In a few cases there is a suggestion of mild hyperthyroidism, but most authors find the B.M.R. within a few points of normal, and the radioactive iodine test normal. Blood cholesterol values seem to fluctuate from as high as 280 to as low as 100 mgs. per cent. Osteoporosis and metastatic calcification is almost universal, yet a high serum calcium and evidence of increased parathyroid activity is only found in some instances. Pomeranz (1948) was able to diagnose a patient radiologically because of the extreme osteoporosis, calcification of the blood vessels and soft tissues, osteoarthritis and the dysharmony between the skeletal and dental age.

The skin changes are superficially like scleroderma, but microscopic examination shows atrophy of the epidermis and flattening of the papillæ. There is no evidence whatever of arteritis, lymphocytic infiltration or œdema, homogenisation or sclerosis of the collagen. The subcutaneous tissues are scanty and lack fat cells, while hair follicles and sweat glands are few in number. The skin is, therefore, atrophic except when exposed to pressure on the feet, insteps, and elbows where hyperkeratosis is found. These areas often break down to ulcers which may have some connection with depositions of calcium. Tannhauser (1945) was the first to point out the distinction and called the condition pseudo-scleroderma. The muscles were found to be swollen with loss of striations by Williams (1949) and in some areas were completely replaced by fibrous tissue. On the other hand they were reported as atrophic by Irwin and Ward (1953).

The high-pitched voice has also been remarked on and in some cases the vocal cords show a crazy paving appearance with white atrophic areas separated by bands of dilated vessels.

The syndrome, although showing variations depending upon the degree of atrophy of the various tissues and attempts at compensation by those less affected, presents an easily recognisable entity. It is remarkable, however, that mental defect does not appear to be a feature in spite of the involvement of the rest of the body. Some biochemical defect, as yet unrecognised, is probably at fault and, while the clinical features are unique, the histology has not been either helpful or specific.

Comment.

This patient had been considered to be a case of hypopituitarism with hypogonadism in association with scleroderma. He had been in hospitals on several occasions for treatment of his leg ulcers and had been thoroughly investigated. All who had seen him had noted that there was something more to it than just hypopituitarism, although the syndrome had not been recognised. There is evidence of some pituitary hypofunction as shown by insulin sensitivity and low gonadotrophins. Low ketosteroids and low blood pressure suggest associated adrenal and genital underaction. Urine at times had shown sugar, but no evidence of diabetes had been found. Blood cholesterol always seemed to have been on the low side and the thyroid function normal. There was no real evidence of parathyroid disfunction, although osteoporosis was present.

In this case we have not been able to obtain a family history. He has no offspring, but had been married.

Naturally he suffered from psychological disability associated with his condition and, as a witness, was not entirely reliable.

I would like to thank Dr. Cotton Kennedy and Mr. D. Neill for their great help and interest with the laboratory investigations, Dr. J. C. Meenan for the photographs, and Dr. J. E. Morison for reporting on the skin biopsy. I am also grateful to Dr. G. Scarlett.

References.

Atkins, L. (1954). *New Engl. J. Med.*, **250**, 1065.

Beath, R. M. (1934). *Brit. J. Radiol.*, **7**, 372.

Brink, A. J., and Findlay, G. H. (1950). *S. Afr. med. J.*, **24**, 318.

Carleton, A. (1943). *Brit. J. Derm.*, **55**, 83.

Irwin, G. W., and Ward, P. B. (1953). *Amer. J. Med.*, **15**, 266.

Oppenheimer, B. S., Kugel, V. H. (1941). *Amer. J. med. Sci.*, **202**, 629.

Pomeranz, M. M. (1948). *Radiology*, **51**, 521.

Tannhauser, S. J. (1945). *Ann. intern. Med.*, **23**, 559.

Werner, C. W. O. (1904). *Uber Kataract in Verbinding mit Sclerodermie. Inaug. Dissert., Kiel.*

Williams, D. I. (1949). *Proc. Roy. Soc. Med.*, **42**, 572.